Claims 39, 56-57 and 60-62 were rejected under 35 USC 112, second paragraph as being indefinite in certain recitations. As for "abnormal amount", this has been changed to a different amount compared to the control to avoid any confusion. Antecedent basis for "said disease state"; "the individual" and "said markers" was present though perhaps in the singular vs. plural form. The claims have been amended to avoid single/plural confusion.

As for the alleged indefiniteness of "the levels of each protein in said proteome" as a protein can have only one level, this is disagreed with because the term "proteome" is a collection of many individual proteins as defined in the specification on page 11. While each individual protein has only one level, the proteome has many "levels", one for "each protein". As for how the levels can be compared, claim 60 was amended to state that they are compared to the levels of the corresponding protein in the control sample. This was implied before and by explicitly stating so should add to clarity. Therefore, the claim language is definite.

Claims 39, 56 and 60-61 were rejected under 35 USC 102(b) as being anticipated by Pleibner et al. The previous claims differed and the present claims differ in several aspects.

All of the claims recite measuring the proteins from a body fluid. Pleibner et al measures proteins from a chunk of heart tissue, which is not a body fluid. This difference is not trivial as stated in the specification on page 11, second paragraph. Body fluids are not the tissue specifically affected by the disease but rather may or may not be indirectly affected. Changes in heart muscle proteins noted by Pleibner et al may not be reflected in body fluids and there is no reason to believe that any proteins, much less the same proteins would be perturbed in the blood.

All claims recite determining a plurality of protein markers/targets whereas Pleibner et al state that they found only one protein, which differed markedly with a p value of <0.05. (Abstract, line 17-19; page 4047, table 2, etc.). One protein is not a plurality of proteins. Furthermore, the newly added claims recite that the differences must have a statistical significance of $p < 0.01$ and $p < 0.001$. Pleibner et al table 2 is entitled "The four most different protein spots between hypertensive and control group..." and shows only <u>one</u> with a significance within the broadest range claimed and none within the

narrowest range claimed. This is all the more significant because the present invention is measuring proteins in indirectly affected tissues rather than those directly affected.

All of the claims recite that the subject providing the body fluid has the various disease states. In Pleibner et al, rats are artificially given high blood pressure by clamping a renal artery. This is an artificial system, which essentially never occurs in nature and thus induces an artificial protein response rather than the abnormal protein abundances resulting from a disease state. Accordingly, Pleibner et al neither teach nor would be expected to achieve the same results as that of the present invention. Certainly, Pleibner et al lack any teaching of using samples from individuals with other diseases.

Claim 39 last paragraph recites determining proteins markers involved in a metabolic pathway of the disease. Pleibner et al provides no evidence any protein found correlates to any metabolic pathway. Pleibner et al does not even analyze the protein spots to identify the protein. While the rejection and the reference state that the spot is located near where the creatine kinase M-chain should be located, Pleibner et al never determined what protein this spot is and did not, actually state what protein(s) is present in the spot. As one can see, the gels have hundreds (or thousands) of spots and a number of other spots are located in the same general area as where the creatine kinase M-chain should be. Without identifying the proteins altered, one cannot make any conclusions about what it is, whether it is involved in any metabolic pathway, have anything to do with a disease or simply be a random artifact of the experiment.

It should also be noted that all of the newly added claims recite features also not found in Pleibner et al.

Claims 57-62 were rejected under 35 USC 103 as being unpatentable over Pleibner et al in view of Chambers et al. Deficiencies in Pleibner et al are discussed above. Chambers adds little other than a review of potential uses for Proteomics. The combination provides no more than an invitation to experiment widely in the field of Proteomics and a hope for results. Applicants agree that the field of Proteomics may yield valuable information and applicants and their competitors already have several other patents in this field. However, none of this suggests that the entire field is closed to new inventions. The present claims are not directed to a general suggestion to do proteomic

experiments, but rather involve a novel protocol used for successfully finding indirect markers and targets in certain specific disease states.

Chambers et al has many of the same deficiencies such as using solid tissue rather than body fluids; see page 280, column 2, lines 20-21; Figure 1, line 1; page 283, second column. Much less for blood derived fluids (claims 76-77) The applications to many diseases such as cancer, neuropathology, cardiovascular disease and microbiology all involve tissues and cells, not body fluids.

Furthermore, neither reference suggests that this approach may be useful for finding targets/markers for obesity, osteoporosis, diabetes or osteoarthritis, (claims 70-71) much less actually show successful results from samples other than those directly affected by any disease processes. Chambers et al lacks any teaching of strongly altered abundances along the lines of claims 66-69.

Still further neither reference alone or in combination suggest using identical twins or the advantages thereof (claims 57, 62).

While some of the sample preparation steps in Chambers et al may be considered a fractionation, neither reference teach specifically removing a predetermined protein without affecting the remainder (claims 72-75). This is particular important with plasma or serum samples where the four proteins removed by immunosubtractive chromatography in the specification examples constitute the vast majority of protein molecules present, thereby providing for easier identification of less abundant proteins.

With so many claimed differences, which are neither taught nor suggested by either reference, it would be unobvious to consider any possible combination as rendering the claimed invention patentable.

CONCLUSIONS

In view of the amendments and comments above, the rejections have been overcome. Reconsideration, withdrawal of the rejections and early indication of allowance are respectfully requested.

The commissioner hereby is authorized to charge payment of any fees under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.500933.

Respectfully submitted,

John E. Tarcza
Reg. No. 33,638

Date: June 18, 2003

Attachments (2): Marked-Up Specification; Marked-Up Claims

John E. Tarcza
Intellectual Property Advisor
Large Scale Biology Corporation
20451 Seneca Meadows Parkway
Germantown, MD 20876
301-354-1200 ext. 1223
301-354-1300 Fax.
E-MAIL john.tarcza@lsbc.com

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an enveloped addressed to:
Assistant Commissioner for Patents
Washington, DC 20231

On June 18, 2003

Typed or printed name of person signing this certificate John E. Tarcza

Signature

Marked up version of page 39, first partial paragraph.

Number 643,675 filed August 24, 2000, now U.S. Patent 6,301,377 and the "IMPRESS" method of U.S. Serial Number [_____] 09/653,363 filed August 31, 2000, now U.S. Patent 6,404,905, Attorney Docket Number 40732. The data regarding the protein spots identified is given in the Tables above and Figures.

39. (amended) A method for finding drug development targets for obesity, osteoporosis, diabetes, osteoarthritis or hypertension comprising;

measuring the level of each protein in a proteome of a [biological sample] **body fluid** containing protein from a subject having **a disease state of** obesity, osteoporosis, diabetes, osteoarthritis or hypertension,

comparing the level of each protein to the level in a control [biological sample] **body fluid**,

determining which proteins are found in a statistically significant [abnormal amount] **different amount compared to the control** thereby indicating them to be protein markers, and

determining which of the protein markers is involved in the same metabolic pathway as said disease state, thereby indicating these to be drug development targets.

56. (amended) The method of claim 39 wherein said [biological sample] **body fluid** and said control [biological sample] **body fluid** are from one or more genetically identical individuals.

57. (amended) The method of claim 56 wherein the [individual is] **individuals are** a human.

60. (amended) A method of identifying [a marker] **markers** diagnostic, prognostic, [or] indicative of

appropriate therapy for a disease state **or monitoring response to therapy**, comprising;

a) obtaining a [biological sample] **body fluid** from a subject having **a disease state of** obesity, osteoporosis, diabetes, osteoarthritis or hypertension,

b) determining levels of proteins in the proteome in said [biological sample] **body fluid**,

c) comparing the levels of each protein in said proteome to levels of **a corresponding** protein in a control [sample] **body fluid** from a subject not having the disease state or a control standard,

d) determining which proteins have statistically significantly higher or lower levels in each [sample] **body fluid**,

wherein said markers have a statistically significantly higher or lower level in a comparison between the two [samples] **body fluid**.

61. (amended) The method of claim 60 wherein said [biological sample] **body fluid** and said control [biological sample] **body fluid** are from one or more genetically identical individuals.

63. (amended) The method of claim 61 wherein the [individual is a] **individuals are** human.

NEW CLAIMS

66. The method of claim 39 wherein statistically significant is determined as a $p<0.01$.

67. The method of claim 66 wherein statistically significant is determined as a $p<0.001$.

68. The method of claim 60 wherein statistically significant is determined as a $p<0.01$.

69. The method of claim 68 wherein statistically significant is determined as a $p<0.001$.

70. The method of claim 39 wherein the disease state is obesity, osteoporosis, diabetes or osteoarthritis.

71. The method of claim 60 wherein the disease state is obesity, osteoporosis, diabetes or osteoarthritis.

72. The method of claim 39 further comprising fractionating the body fluid before said measuring the level of each protein in a proteome.

73. The method of claim 72 wherein said fractionating specifically removes one or more preselected proteins from the body fluid.

74. The method of claim 60 further comprising fractionating the body fluid before said determining levels of proteins in the proteome.

75. The method of claim 74 wherein said fractionating specifically removes one or more preselected proteins from the body fluid.

76. The method of claim 39 wherein the body fluid is a fraction of blood.

77. The method of claim 60 wherein the body fluid is a fraction of blood.